

REMARKS

A Request for Continued Examination accompanies this Response. Claims 1-6, 17 and 18 are pending in the present application and stand rejected as lacking enablement under 35 U.S.C. §112, first paragraph.

The present claims are directed to a method for inhibiting the overactivity of phagocytes or lymphocytes in an individual by administering an effective amount of a lignan of the specified formula. The phagocytes are specified as either (i) neutrophils or (ii) cells of myeloid origin and the lymphocytes are specified as T-lymphocytes. When the phagocytes are neutrophils, the lignan is specified as hydroxymatairesinol or matairesinol or a mixture thereof. When the phagocytes are cells of myeloid origin, the lignan is specified as enterolactone or hydroxymatairesinol or a mixture thereof. When the lymphocytes are T-lymphocytes, the lignan is specified as hydroxymatairesinol, matairesinol or enterolactone or a mixture thereof. The present claims are not directed to the treatment of any diseases.

In the Advisory Action, the Examiner contends that the specification is enabling for the following:

(i) a method of inhibiting oxidative burst and myeloperoxidase by administering individual lignan hydroxymatairesinol or matairesinol to neutrophils *in vitro*;

(ii) pretreatment of Jurkat T cells with either hydroxymatairesinol, enterolactone or matairesinol increases Fas mediated apoptosis by increasing Fas receptor expression on T cells *in vitro*;

(iii) enterolactone or matairesinol treatment inhibits LPS mediated TNF alpha production by monocytes *in vitro*.

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However, the Examiner contends that the specification is not enabling for the scope of the claims as written.

First, the Examiner contends that the specification fails to teach a "mixture" of lignans for the claimed method of inhibiting overactivity of phagocytes or lymphocytes. It is submitted that the Examiner is in error in this rejection. The legal question of enablement involves an assessment of whether a patent disclosure would have enabled one of skill in the art at the time the application was filed, to make and use the claimed invention without undue experimentation. See Adang v. Fischhoff, 62 U.S.P.Q.2d 1504 (Fed. Cir. 2002). A specification complies with the enablement requirement, even if it requires the skilled artisan to engage in a "reasonable" amount of routine experimentation, so long as such experimentation is not "undue." See In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

In In re Wright, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993), the Federal Circuit made clear that the PTO has the burden of providing a reasonable explanation of why the specification does not enable. There must be some reason to doubt the objective truth of the specification statements. In re Marzocchi, 169 USPQ 367 (CCPA 1973). Furthermore, Applicants submit that the Examiner has not provided acceptable evidence inconsistent with the contested statements in the specification.

[I]t is incumbent upon the Patent Office, whenever a rejection on this basis [i.e. doubt of the objective truth of statements in the specification] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go through the trouble and expense for supporting his presumptively accurate disclosure.

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169 U.S.P.Q. at 370. It is submitted that the Examiner has not provided any reasonable basis to doubt the objective truth of the specification that the specified mixtures of the specified lignans can be used.

The Examiner admits that the specification is enabling for inhibition of myeloperoxidase activity and oxidative burst by administering individually hydroxymatairesinol or matairesinol to neutrophils but fails to teach a "mixture." It is Applicants' position that it would not require undue experimentation, rather reasonable experimentation, from one of skill in the art to obtain a "mixture," as claimed in the present invention. As claimed, a "mixture" is of a very limited number of lignans. For instance, (i) requires a "mixture" of only two lignans: hydroxymatairesinol and matairesinol. In claim 1, (ii), the "mixture" is of two lignans as well: enterolactone and hydroxymatairesinol. Finally, in claim 1, (iii) the "mixture" requires three lignans: hydroxymatairesinol, matairesinol, and enterolactone. Applicants submit that if one lignan works, and the other lignan works, one of ordinary skill in the art would recognize that a "mixture" of lignans would work. But more importantly, at the time the application was filed, one of skill in the art would have been able to construct a "mixture" of lignans as claimed without undue experimentation, merely by pipetting into a test tube the components required. In fact, a patent need not teach, and preferably omits, what is well known in the art. See Spectra Physics, Inc. v. Coherent, Inc., 3 U.S.P.Q.2d 1537 (Fed. Cir. 1987). Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Second, the Examiner contends that the specification is not enabling because it lacks an *in vivo* working example demonstrating that each lignan has inhibitory activity *in vivo*. One reason provided by the Examiner to support

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his position is that the specification teaches that pretreating Jurkat T cells with either hydroxymatairesinol, or enterolactone or matairesinol increases Fas mediated apoptosis and increases Fas receptor expression on T cells *in vitro*, which is just the opposite of inhibiting the "overactivity of lymphocytes." The Examiner has incorrectly interpreted this disclosure in the specification. First, the background of apoptosis and increased Fas-expression is presented in paragraphs 0012 through 0015 of the specification. These mechanisms are effective in the elimination of T-cells. In example 2, it is clearly shown that increase of Fas-induced apoptosis and increase of Fas-expression lead to inhibition of overactivity of T-lymphocytes. See specification at paragraph 0055. Thus, this basis for the Examiner's rejection is incorrect and does not support the rejection.

More importantly, however, is the fact that an *in vitro* or *in vivo* example in the specification, in effect constitutes a "working example ... if that example "correlates ... with a disclosed or claimed method invention. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 224 USPP 739, 747 (Fed. Cir. 1985).

The Examiner, in response to Applicants' previous arguments that the Dandona *et al.* and Devaraj *et al.* references demonstrate a reasonable expectation of success between *in vitro* and *in vivo* effects in a model system looking at antioxidant effects, considers the references "irrelevant to the claimed invention" because they involve disclosure of drugs having different structures. Furthermore, in response to our arguments regarding the Pool-Zobel *et al.* reference, the Examiner argues that just like the instant application, the Pool-Zobel *et al.* reference does not teach how to extrapolate *in vitro* experiments to *in vivo* methods of inhibiting overactivity of phagocytes or

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lymphocytes in all individuals. It is Applicants' position that they are not required to show how to extrapolate *in vitro* experiments to *in vivo* methods of inhibiting overactivity of phagocytes or lymphocytes in all individuals, especially where it was known in the art. It is submitted that the Examiner is in error in his interpretation of these references, and Applicants reasons for their submission.

Applicants did not submit the Dandona *et al.* and Devaraj *et al.* references in order to prove *in vivo* activity for the claimed invention. Rather, Applicants submitted the Dandona *et al.* and Devaraj *et al.* references as proof that one can reasonably expect success between *in vitro* and *in vivo* effects in a model system. There is a good predictability of *in vivo* effects of a drug once corresponding effects have been show *in vitro*, as demonstrated by Dandona *et al.* and Devaraj *et al.*

As stated in Applicants' previous responses, Dandona *et al.*, demonstrates that the drug carvedilol has antioxidative effects in humans *in vivo*. In the introduction, first paragraph, Dandona *et al.* states that the same drug (Carvedilol) has been shown to possess antioxidative properties, namely scavenging peroxy and hypochlorous radicals in chemical systems *in vitro* (the *in vivo* study is shown in Aruoma, O.I., *Gen Pharmacol.* **28**:269-272 (1997), reference number 3 in the listing at the end of the text). Devaraj *et al.*, demonstrates that alpha tocopherol (Vitamin E) has antioxidative properties in humans *in vivo*. The agent decreases the release of reactive oxygen species, lipid oxidation, interleukin-1-beta secretion and monocyte adhesion to endothelium. This agent had earlier been shown to possess antioxidative properties *in vitro* (see Burton *et al.* *Ann. NY Acad. Sci.* **570**:7-22 (1989), reference number 55 in the listing at the end of the text).

Both of these references show that, contrary to the Examiner's contention, there is a clear correlation between test results *in vitro* and effects for the tested drugs *in vivo*. Furthermore, Pool-Zobel *et al.* does not contradict the teachings and expectation of success in the art shown by the Dandona *et al.* and Devaraj *et al.* references. Pool-Zobel *et al.* only shows *in vitro* data and thus cannot contradict the art cited by Applicants.

The Examiner contends that the Dandona *et al.* and Devaraj *et al.* references are not relevant to Applicants' position because they describe the structurally different drugs carvedilol and tocopherol, not hydroxymatairesinol, matairesinol, and enterolactone. The fact that these references do not describe the three lignans as claimed, is not relevant to the question of predictability with respect to *in vitro* and *in vivo* activity. These references clearly demonstrate that a skilled artisan would predict with a reasonable expectation of success, i.e., with reasonable probability (Cross, supra), that compounds which are active in the *in vitro* model are active *in vivo*. Thus, a skilled artisan would predict with a reasonable expectation of success that the claimed lignans having the *in vitro* activity demonstrated in the present application for the claimed cell types would have *in vivo* activity with respect to these same cell types. Cross, supra.

Third, the Examiner contends that the specification is not enabling for treating any disease. The Examiner acknowledges that the specification discloses that it is a further object of the invention to inhibit the overactivity of T lymphocytes by inducing their self-destroying activity, and thereby lowering the risk, and prevention or treatment of diseases or conditions due to this mechanism. The Examiner also states that the specification discloses conditions which can be treated or prevented by administering

hydroxymatairesinol, matairesinol or enterolactone as allergic conditions, autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, asthma, psoriasis, type I and type II diabetes, rejection due to tissue transplant, atherosclerosis, and multiple sclerosis, Alzheimer's disease, HIV, and AIDS. However, the Examiner reaches the conclusion that the claims are directed to the treatment of any disease and argues that given the indefinite number of diseases, coupled with the lack of *in vivo* working examples, and the idea that different lignans have different effects on different cell types, it is unpredictable which overactivity of phagocytes or lymphocytes that the claimed method can inhibit *in vivo*. Thus, until a specific overactivity of phagocytes or lymphocytes is associated with a particular condition that the claimed method has been demonstrated *in vivo*, the specification invites one skilled in the art for further experimentation to arrive at the claimed invention.

Applicants reiterate that the claims are directed to inhibiting the overactivity of phagocytes or lymphocytes. The claims are not directed to the treatment of any diseases because such claims have been canceled in view of the Examiner's restriction requirement. In the requirement for restriction, the Examiner concluded that the present claims for inhibiting overactivity of phagocytes or lymphocytes are patentably distinct from claims for treating diseases, such as those listed by the Examiner. Since the present claims (a) are patentably distinct from the disease treatment claims and (b) are limited to inhibiting overactivity of phagocytes or lymphocytes, the Examiner's contention concerning the lack of enablement for the treatment of any disease is not relevant to the enablement of the invention as claimed.

Applicants have established with their discussion above and in past responses that a skilled artisan has a reasonable expectation of success

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between *in vitro* and *in vivo* effects in a model system looking at antioxidative effects.

The Examiner fails to present any acceptable scientific evidence or reasons to doubt the objective enablement of the specification for the method for inhibiting the overactivity of the specified phagocytes or lymphocytes by the administration of hydroxymatairesinol, matairesinol and enterolactone. Thus, it is Applicants' position that a proper case for lack of compliance with the enablement provision of 35 U.S.C. §112, first paragraph has not been established. Furthermore, the references cited by Applicants have established that the area is not unpredictable, especially with respect to *in vitro* and *in vivo* activity, and therefore support the objective enablement of the specification. These references -- even though they discuss compounds other than the three lignans at issue -- demonstrate the reasonable expectation of success in the art for the claimed invention. Applicants have provided examples in the specification of the claimed activity of the claimed lignans with respect to the claimed cell types. Applicants have provided guidance in the specification as to which lignans to use with which cell types. The claims are narrowly construed only to the inhibition of overactivity of certain claimed cell types by certain claimed lignans. At issue for an enablement rejection is not whether any experimentation would be required, but whether such experimentation would be undue. All of the facts detailed above clearly establish that one of skill in the art can practice the claimed invention without an undue amount of experimentation, and thus the claimed invention is enabled.

In view of the above remarks, it is submitted that claims 1-6 and 17-18 are fully enabled by the specification. Withdrawal of this rejection is requested.

It is also submitted that the present claims satisfy the requirements of

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the patent statutes and are patentable over the prior art. Reconsideration and early notice of allowance are requested. The Examiner is invited to telephone the undersigned in order to expedite prosecution of the present application.

Respectfully submitted,

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